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Comparative Effectiveness Analysis and Statistical Methodology

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Abstract

The purpose of comparative effectiveness analysis is ordinarily defined as a means to compare the benefits of drug A versus drug B. However, particularly in relation to cancer drugs, there is only drug A. Therefore, comparative effectiveness analysis tends to compare drug A to a quality adjusted threshold value, with a frequent conclusion that the cost of the drug is not worth the additional life. Ordinarily, a societal perspective is used to deny the drugs, since the additional life may be worth the drug cost for the patient. The British organization, the National Institute for Clinical Excellence (NICE) has denied many cancer drugs to their patients. The Centers for Medicaid and Medicare want to initiate a similar process, denying treatments that exceed a quality adjusted price of $50,000. There are similar provisions in the Healthcare Reform Act. With the emphasis upon medications, medical procedures are not as subject to this comparative effectiveness scrutiny; procedures can frequently exceed the cost of medication treatments. However, each medication is considered separately; no analysis examines the total contribution of the treatment to the overall cost of healthcare. The Medical Expenditure Panel Survey can be used to find the total contribution of costs resulting from a patient treatment. We will demonstrate using SAS techniques how we can investigate the contribution of a procedure to the total cost of healthcare.

Introduction

The National Health Service in Britain has been using comparative effectiveness analysis for quite some time. NICE stands for the National Institute for Health and Clinical Excellence. This organization has defined an upper limit on treatment costs, and if the cost exceeds this pre-set limit, then the treatment is denied. It does not matter if the drug is effective or not. That means that there are many beneficial drugs that are simply not available to patients in Britain. fully 25% of cancer patients are denied effective chemotherapy medications.

NICE is not comparing drug A to drug B. Instead, the organization compares the cost of a drug to the value the organization places on your life. If it costs too much to keep you alive given your value, or to improve your life, then you are denied treatment. While you may believe that such denial will not come to the United States, it already has. Oregon has become notorious in its Medicaid benefit, denying cancer drugs to patients, but making the same patients aware that assisted suicide is available. Oregon will not make available drugs that can prolong a patient's life; it will make available a drug to end it (which will then save additional medical costs). Currently, pharmaceutical companies have been subsidizing Oregon's Medicaid by providing these drugs to patients who have been denied by Medicaid. (Smith 2009) It has been suggested that euthanasia is cheaper than end of life care, and more cost-effective than treating many patients with terminal illnesses. (Sprague 2009) Just recently, the Food and Drug Administration has considered retracting approval of a chemotherapy drug for breast cancer on the basis of cost effectiveness rather than effectiveness.

A comparative effective analysis starts with the perceived patient's utility given the disease burden. The QALY, or quality of life-adjusted years is an estimate of the number of years of life gained given the proposed intervention. Each year of perfect health is assigned a value of 1.0. A patient in a wheelchair is given a correspondingly lower value as is a patient who is elderly; this value is not clearly defined and is rarely based upon patient input.

Consider an example. Suppose a cancer drug for patients with liver cancer allows a patient to live an average of 18 months compared to not using the drug. However, as with most cancer drugs, there are potent side effects. Suppose that the analyst decides that the quality of life is only 40% of perfect health (giving a weight of 0.4). Then the drug gives 1.5*0.4=0.6 QALYs to the patient. Suppose that at the initial introduction of this drug, it costs $1000 per month, or about $18,000 for the anticipated additional life of the patient. Then the cost per QALY is equal to 18,000/0.6=$30,000 per year of life saved. According to the NICE organization, this drug then is too costly regardless of the fact that there is no comparable drug that is effective in prolonging the patient's life. However, suppose the analyst uses a measure of 60% of perfect health. Then the drug gives 1.5*0.6=0.9 QALYs to the patient at a cost of $20,000, which brings the amount closer to the pre-set value defined by NICE. Therefore, this definition of a scale of perfect health is of enormous importance. In fact, NICE has denied such a cancer drug because of its cost.
If a person is otherwise young and healthy and a drug costs $10,000 per year, then the QALY is $10,000. However, if a patient is older and has a chronic condition, then that patient's utility may be defined as exactly half that of a young

and otherwise healthy person. In that case, the QALY is $20,000 for the same drug. If the patient is old and has two or more chronic conditions, then the patient's utility could be defined as 25% that of a young and healthy person. In that case, the QALY IS $40,000 per year of life saved. By defining $15,000 as the upper limit for treatment, it is easy to see how the definition of a person's utility can be used to deny care to the elderly.

However, the cost of treating the disease is not restricted to the cost of medications. Therefore, we must look at all aspects of treatment, including physician visits, hospital care, and home health care. We must also look at the impact of patient compliance on the overall cost of healthcare. If patients have specific diseases that can be treated, but who do not use the treatment, then outcomes will not be the same compared to patients who do comply. Also, patients who switch treatments may suffer from adverse events of the first treatment that are not present in the second treatment. Therefore, we must examine the totality of patient care.

Use of SAS to Combine Information

In claims data, prescriptions are separated from inpatient and outpatient treatments as well as office visits and home health care. Because all of this information is stored in different files in a one-to-many relationship with a patient's identification number, the most important aspect of using these databases is to convert them to a one-to-one relationship after filtering down to the condition under study. We take advantage of the data step and the use of summary statistics to do both. Each patient claim is identified by an ICD-9 code as to the primary reason for the medication or treatment. Osteoporosis, for example, is identified by the codes, 733.0x where x can be a digit from 0 to 9 (http://icd9cm.chrisendres.com/). Each of the datasets has a column for the primary code. We can use an if...then statement in a data step to isolate patients with a specific condition.

Once the different data sets have been filtered down to a specific condition, we need to convert them to a one-to-one relationship. We use the following code:

```
TITLE;
TITLE1 "Summary Statistics";
TITLE2 "Results";
FOOTNOTE;
FOOTNOTE1 "Generated by the SAS System (&_SASSERVERNAME, &SYSSCPL) on
%TRIM(%QSYSFUNC(DATE(), NLDATE20.)) at %TRIM(%SYSFUNC(TIME(), NLTIMAP20.))";
PROC MEANS DATA=WORK.SORTbyID
       FW=12
       PRINTALLTYPES
       CHARTYPE
       NWAY
       VARDEF=DF
             MEAN
             STD
             MIN
             MAX
             N      ;
       VAR TOTTCH06 OBTTCH06 OPVTCH06 OPOTCH06 AMETCH06 AMATCH06 AMTTCH06
AMTOTC06 ERDTCH06 ZIFTCH06 IPFTCH06 DVTOT06 DVOTCH06 HHNTCH06 VISTCH06 OTHTCH06
RXTOT06;
       CLASS cost_Sum /    ORDER=UNFORMATTED ASCENDING;

RUN;
```

We then choose one of the datasets to serve as the primary set and merge the datasets using a left join or a right join, depending upon the order of the data sets, using PROC SQL.

```
PROC SQL;
   CREATE TABLE SASUSER.QUERY_FOR_SUMMARYOFCONDITIONS_SA AS
         SELECT t1.patientID,
             t1.remaining variables from dataset,
             t2.variables from second dataset
FROM claims.summaryofconditions AS t1 RIGHT JOIN claims.h105 AS t2 ON
(t1.patientID = t2.patientID);
```

```
QUIT;
```

We will demonstrate how the results can be used for a direct comparison of costs. In addition, we have to be concerned about whether medication is discontinued, or if the patient switched to a different one. We use the following code:

```
proc transpose data=medications out=medicationbyid
     prefix=med_;
    id patientid;
run;
```

Because the database has accurate dates for prescriptions, we can investigate in more detail the occurrence of medication switching using survival data mining. In order to do this, we need to transpose both date and medication. Doing a similar code to transpose the medication date, we then merge the two transposed datasets together so that both medication and date are in the same dataset. We then need to search for the first prescription that involves switching, and the date when the switching occurs. If no switching occurs, we define the final date as a censoring value. The coding used is:

```
data sasuser.survivaldata;
  set medicationbytranspose;
  array meds(379) med_1 - med_379;
  array dates(379) date_1 - date_379;
do j=1 to 379;
    if dates(j)=. then dates(j)='31dec2004'd;
       censor=1;
  end;
  do i=1 to 379;
    if i=1 then temp=meds(i);
    if meds(i) ne temp then do;
      med_num=i;
      date_num=dates(i);
       medchange=meds(i);
       censor=0;
      i=379;
    end;
  end;
run;
```

where 379 is the largest number of prescriptions for any one patient. These can involve more than just the medications under study because of co-morbidities, so we also need to isolate to the specific medications involved.

The censoring variable can be modified to search for specific endpoint medications. For example, if we want to know whether the change is equal to the drug, Boniva, then we define Boniva=0 if medchange='Boniva' and =1 otherwise. We also convert the date of switching to a SAS date. The code to do this is added to the data step above:

```
if date_num = . then date_num='12dec2006'd;
if (medchange eq ' ') then censor=1;
if (medchange eq 'Drug_1') then drug_1=0;
else drug_1=1;
if (medchange eq 'Drug_2') then Drug_2=0;
else drug_2=1;
finaldate=input(newlastdate,anydtdtm17.);
format finaldate datetime17.;
final=datepart(finaldate);
        format final date9.;
```

Then we apply survival analysis, stratifying by the initial medication using the start of the year, 2006, as time=0. In doing this, we make the assumption that future medication choice depends on the present medication and not on the past medications. The code is

```
PROC LIFETEST DATA=sasuser.survival data ALPHA=0.05
;
        BY medchange;
        STRATA med_1;
        TIME Days * censor (1);

RUN;
```

Treatment of Osteoporosis

In this example, we combine different datasets taken from the Medical Expenditure Panel Survey. We want to see if patients taking different medications have different types of other treatments that can increase costs. We first look at the costs for each type of care: medications, inpatient, outpatient, office visits, and home health care. We also look at the issue of patient compliance in relation to the medications. It is possible that patients are more likely to comply with one medication over another, and compliance might reduce the overall costs in terms of treatment. Table 1 gives the costs of the medications used to treat osteoporosis along with the different payers.

Table 1. Total Cost for Osteoporosis Medications

year	N Obs	Variable	Mean	Sum	N
2005	3733	selfpay	50.1955746	187380.08	3733
		medicare	2.9947924	11179.56	3733
		medicaid	10.4126493	38870.42	3733
		private	27.2414894	101692.48	3733
		va	0	0	3733
		total	94.2722127	351918.17	3733
2006	4179	selfpay	36.7708279	153665.29	4179
		medicare	27.6511079	115553.98	4179
		medicaid	2.7505288	11494.46	4179
		private	17.6373654	73706.55	4179
		va	0	0	4179
		total	88.2418689	368762.77	4179

It indicates that the average prescription went from $50 self-pay to $36 while Medicare again increased 10-fold and Medicaid paid 1/3 of the amount in 2006 that it paid in 2005 for these medications. Private insurance declined considerably from $101,692 in 2005 to $73,707 in 2006 for this cohort of patients. The results suggest that most of the patients prescribed these medications are in the Medicare eligible population. The patients just shifted payment for their continuing medication.

Table 2 gives the frequency count for the medication, Actonel, which is a once-a-week prescription. In a year's time, there should be 12 prescriptions with each prescription equal to 4 doses. Possibly, there are 90-day prescriptions of 12 tablets, so we need to take this into consideration as well. We do this by computing the product of the frequency of the prescription by the average quantity by patient. Note that the most frequent value is for just one prescription. The patients who get just one prescription most probably had difficulty with the medication and discontinued its use.

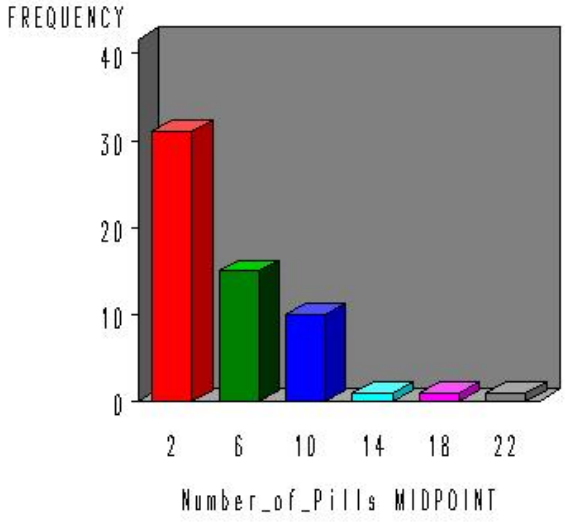
Table 2. Frequency Count for Number of Actonel Prescriptions

FREQ	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1	23	20.91	23	20.91
2	13	11.82	36	32.73

FREQ	Frequency	Percent	Cumulative Frequency	Cumulative Percent
3	10	9.09	46	41.82
4	13	11.82	59	53.64
5	9	8.18	68	61.82
6	8	7.27	76	69.09
7	7	6.36	83	75.45
8	6	5.45	89	80.91
9	6	5.45	95	86.36
10	1	0.91	96	87.27
11	5	4.55	101	91.82
12	3	2.73	104	94.55
13	3	2.73	107	97.27
15	1	0.91	108	98.18
16	2	1.82	110	100.00

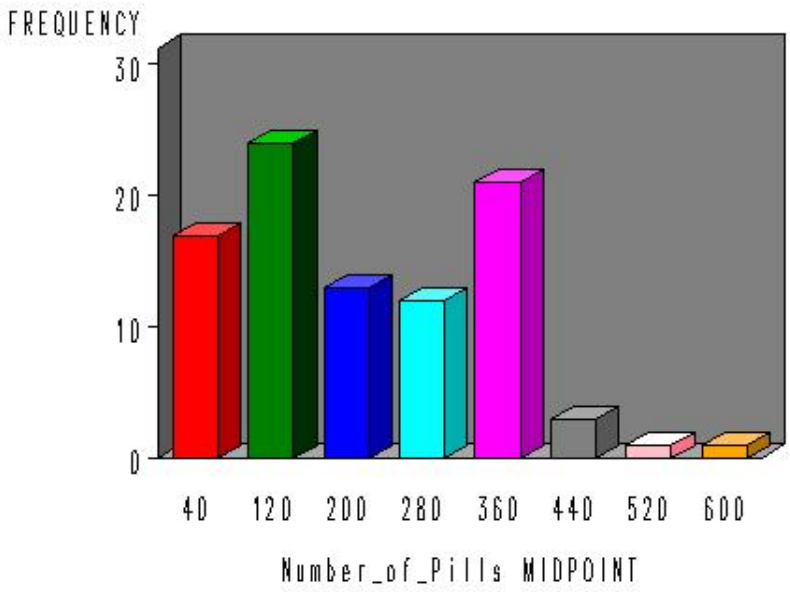
Figure 1 gives the spread of the number of doses for Boniva. Boniva is taken once per month. In a year's time, there should be 52/4 or 13 prescriptions per patient; however, only 6 patients have achieved that number.

Figure 1. Number of Doses for Boniva



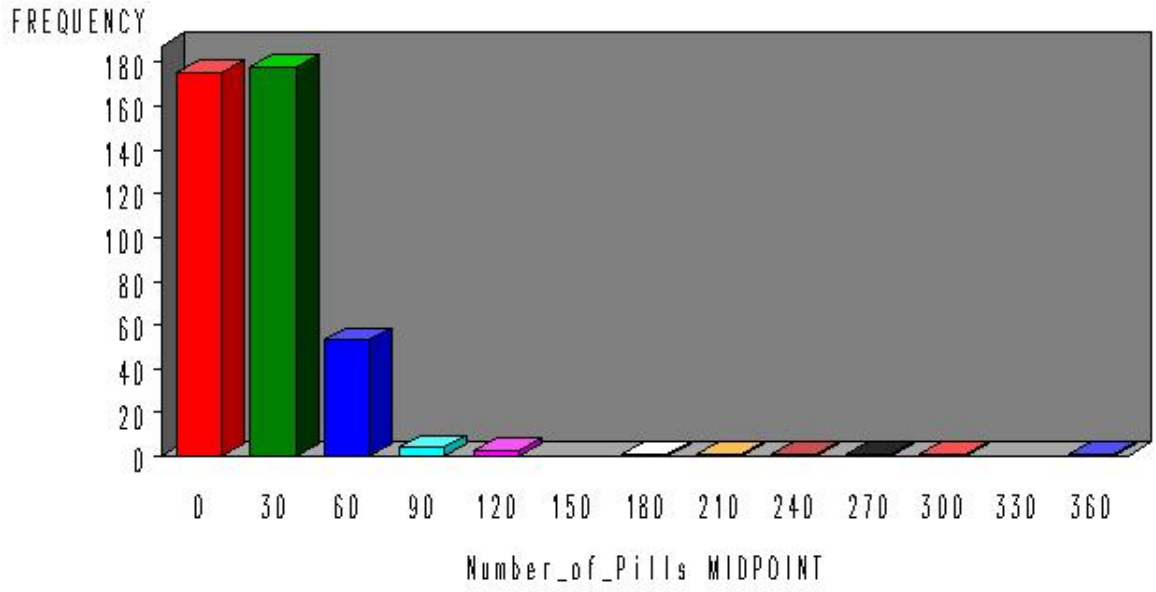
The mode in Figure 1 is for 4 doses or less when it should be for 12 or 13. Again, it does not appear that patients are taking the full medication. It is possible that the patients are switching medications because of adverse effects, so we need to take switching into consideration as we define compliance.

Figure 2. Number of Doses for Evista



Evista is used daily, which suggests that a patient should have approximately 365 doses in a year's time. While there are many who have that number of doses, there are many more who do not. Again, it suggests a lack of compliance with the medication requirements.

Figure 3. Number of Doses for Fosamax



This medication, too, should have 52 doses in a year, although there is a daily dose (which appears to be taken by very few patients). There are some extreme outliers, but most patients are getting less than the 52 doses.
While this preliminary investigation indicates that most of the patients are not in compliance, this result can be misleading. If a patient switches from Actonel to Fosamax during the middle of the year, these patients will appear to

be out of compliance for both medications. Therefore, we must change the observational unit to reflect the total doses for each drug. First, we separate the patients with more than one medication from those with exactly one medication. Table 3 shows the number of patients who switched medications. The number is fairly small. It is sufficiently large so that patients who switch need to be taken into consideration when defining compliance. Note that most of the switching is to Fosamax.

Table 3. Second Medication and Number Who Switched

Recode_RXNAME	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Boniva	5	15.15	5	15.15
Evista	1	3.03	6	18.18
Fosamax	27	81.82	33	100.00

In order to work with medication combinations, we first need to standardize the value. Therefore, we compute a simple ratio for each medication taken, $c(med_i)$=number of doses prescribed/number of doses needed for full compliance. Then we add the sum of $c(med_i)$ for each medication. For example, suppose a patient takes Fosamax for 2/3 of a year and Boniva for the remaining 1/3 of a year. Then, compliance for Fosamax=36/52 and compliance for Boniva=3/12 for that patient. The sum of these values is equal to 36/52+3/12=0.69+0.25=0.94, or very close to one, the ideal identified as full compliance. Finally, we have to make certain that we distinguish between a once-a-day dose and a once-a-week dose. A patient who has 240 doses is on a once-a-day prescription.

We also want to look in the patient conditions listed with the prescriptions for these patients with medications for osteoporosis to ensure that they have been properly diagnosed. Therefore, we consider the ICD9 codes that are associated with each of the medications. For Actonel, there are 646 (out of a total of 996) primary codes given as 733, or Other disorders of bone and cartilage. The specific codes for osteoporosis are 733.01 (Senile osteoporosis or postmenopausal osteoporosis), V17.81 (Osteoporosis), 733.02 (Idiopathic osteoporosis), 733.03 (Disuse osteoporosis), 733.0 (Osteoporosis), and 733.00 (Osteoporosis, unspecified). However, there are other primary patient conditions listed for Actonel that include 714 (Rheumatoid arthritis and other inflammatory polyarthropathies), 715 (Osteoarthrosis and allied disorders), 716 (Other and unspecified arthropathies), 718 (Other derangement of joint), and 719 (Other and unspecified disorders of joint). Actonel is not approved for arthritis and is not considered effective for its treatment. It is possible that arthritis is primary and osteoporosis is secondary as a patient condition. It is also possible that Actonel is used off-label to treat arthritis. However, 733 is not listed as a secondary ICD9 code for Actonel. Either the Actonel is misprescribed, or the ICD9 code is inappropriately listed, or the use is off-label. Evista similarly has 296 out of 690 primary ICD9 codes listed as 733, but unlike Actonel, it has 5 secondary codes also listed as 733. While there are also diagnoses listed for arthritis (715-716), there are 88 primary codes for V68 (Encounters for administrative purposes). This code suggests that the purpose of the encounter was to write a new prescription for a recurring medication.

For Fosamax, there are 1531 primary codes out of 2009 for osteoporosis. There are an additional 88 primary codes for arthritis, 46 primary codes for V68, and 61 for V82 (Special screening for other conditions). In contrast, none of the primary codes for estrogen are for osteoporosis or arthritis. The primary code listed is for 627 (Menopausal and postmenopausal disorders). It suggests that the estrogen prescriptions are not for osteoporosis.
We want to look at the relationship between the level of compliance to the need for treatment for bone fractures that result from the condition of osteoporosis. The number of such patients is quite small; 12 inpatients and 19 outpatients are identified as having treatment for bone breaks, while also having the condition of osteoporosis.

Table 4. Osteoporosis Medications by Inpatient Fractures

Row number	Revised RXName	STRENGTH OF Rx/PRESCR MED DOSE	QUANTITY OF Rx/PRESCR MED_Sum	3-DIGIT ICD-9-CM CODE	3-DIGIT ICD-9-CM CODE	3-DIGIT ICD-9-CM CODE
1	Actonel	35	12	821, Fracture of other and	-1	-1

Row number	Revised RXName	STRENGTH OF Rx/PRESCR MED DOSE	QUANTITY OF Rx/PRESCR MED_Sum	3-DIGIT ICD-9-CM CODE	3-DIGIT ICD-9-CM CODE	3-DIGIT ICD-9-CM CODE
				unspecified parts of femur		
2	Actonel	35	12	821, Fracture of other and unspecified parts of femur	-1	-1
3	Fosamax	70	90	822, Fracture of patella	-1	-1
4	Evista	60	150	724, Other and unspecified disorders of back	733, Other disorders of bone and cartilage	807, Fracture of rib(s), sternum, larynx, and trachea
5	Actonel	35	24	827, Other, multiple, and ill-defined fractures of lower limb	-1	-1
6	Fosamax	70	4	808, Fracture of pelvis	922, Contusion of trunk	-1
7	Fosamax	70	28	820, Fracture of neck of femur	707, Chronic ulcer of skin	-1
8	Fosamax	70	12	041, Bacterial infection in conditions classified elsewhere and of unspecified site	805, Fracture of vertebral column without mention of spinal cord injury	787, Symptoms involving digestive system
9	Fosamax	70	8	824, Fracture of ankle	-1	-1
10	Fosamax	35	24	824, Fracture of ankle	-1	-1
11	Actonel	35	12	812, Fracture of humerus	-1	-1
12	Fosamax	70	4	820, Fracture of neck of femur	812, Fracture of humerus	814, Fracture of carpal bone(s)

Note that for patient #8, the primary code is for infection; it is the secondary code that reveals the bone fracture related to the infection. This problem of infection is always related to orthopedic treatments.

The patients taking Actonel in this group appear to be complying with the number of doses for a once a month treatment. The patients treated with Fosamax do not seem to be complying with the medication. If this is the case (and as shown previously, it is also true for patients generally prescribed the medication), it would be worthwhile to determine just why patients are not complying with the medication and how compliance can be improved.
This table does suggest that there are patients at high risk for fractures who are not complying with their medications. We can see if this remains the case for outpatient visits for fractures (Table5).

Table 5. Osteoporosis Medications by Outpatient Fractures

Row number	RevisedRXName	STRENGTH OF Rx/PRESCR MED DOSE)	QUANTITY OF Rx/PRESCR MED _Sum	3-DIGIT ICD-9-CM CODE	3-DIGIT ICD-9-CM CODE	3-DIGIT ICD-9-CM CODE
1	Fosamax	35	4	805, Fracture of vertebral column without mention of spinal cord injury	-1	-1
2	Fosamax	70	12	825, Fracture of one or more tarsal and metatarsal bones	-1	-1
3	Fosamax	70	156	824, Fracture of ankle	-1	-1
4	Fosamax	70	156	824, Fracture of ankle	-1	-1
5	Fosamax	70	156	824, Fracture of ankle	-1	-1
6	Fosamax	70	156	824, Fracture of ankle	-1	-1
7	Fosamax	70	156	824, Fracture of ankle	-1	-1
8	Fosamax	70	156	824, Fracture of ankle	-1	-1
9	Fosamax	70	156	824, Fracture of ankle	-1	-1
10	Fosamax	70	156	824, Fracture of ankle	-1	-1
11	Fosamax	70	156	824, Fracture of ankle	-1	-1
12	Fosamax	70	156	824, Fracture of ankle	-1	-1
13	Fosamax	70	156	824, Fracture of ankle	-1	-1

Row number	RevisedRXName	STRENGTH OF Rx/PRESCR MED DOSE)	QUANTITY OF Rx/PRESCR MED _Sum	3-DIGIT ICD-9-CM CODE	3-DIGIT ICD-9-CM CODE	3-DIGIT ICD-9-CM CODE
14	Fosamax	70	156	824, Fracture of ankle	-1	-1
15	Actonel	30	32	823, Fracture of tibia and fibula	-1	-1
16	Actonel	30	32	823, Fracture of tibia and fibula	-1	-1
17	Actonel	30	32	823, Fracture of tibia and fibula	-1	-1
18	Fosamax	70	4	820, Fracture of neck of femur	812, Fracture of humerus	814, Fracture of carpal bone(s)
19	Fosamax	70	4	820, Fracture of neck of femur	812, Fracture of humerus	814, Fracture of carpal bone(s)

There is a red flag on the 156 doses of Fosamax to consider; this patient is taking the daily treatment. This list also suggests that patients receive multiple follow up visits for treatment and there are actually just 5 patients in the sample receiving outpatient treatment for fractures.

It would be of interest to determine whether patients who are taking the medications just as a preventative measure to avoid osteoporosis are the ones with limited compliance compared to patients who already have the disease, and who have complications related to the disease. It is said that “an ounce of prevention is worth a pound of cure”. However, if the patients do not accept the prevention, it will do little good.

To examine some of these potential problems, we look to the physician visits and laboratory tests datasets restricted to the patients prescribed osteoporosis medications.

Table 6. Treatment Performed in Physician Visit by Medication (Percent of Patients)

Treatment Performed	IV Therapy	Lab Tests	X-Rays	MRI/CATSCAN	Medication Prescribed
Actonel	1.20	13.08	10.94	15.97	3.38
Boniva	0	13.54	3.09	3.09	4.64
Evista	0	22.49	4.54	13.84	6.51
Fosamax	0.22	18.88	6.72	11.58	4.22
	EKG	**EEG**	**Other Test**	**Surgical Procedure**	
Actonel	3.45	0.26	16.34	7.45	
Boniva	2.04	0	4.51	6.80	

	EKG	EEG	Other Test	Surgical Procedure	
Evista	3.30	0	24.21	21.51	
Fosamax	2.24	0.50	20.72	11.84	

There are differences in the percentage of patients with the type of treatment given the differerent medications. Patients taking Actonel are much more likely to have an X-Ray or an MRI; those taking Boniva are much less likely. It could be that patients with more serious conditions are given Actonel while Boniva is used more for prevention; or it could be that physicians prescribing Actonel are more knowledgeable about needed follow up to guard against side effects. It could also mean that patients taking Actonel are more likely to be tested for fractures. The EKG and EEG are heart-related, and are more likely with Actonel and Evista compared to Boniva and Fosamax. Surgical procedures, too, are more likely with Evista. Therefore, there are additional consequences that are related to the medication choice.

Of course, this is a non-terminal, treatable disease. Terminal illnesses will always be cheaper not to treat. If not treated, the patient dies and is removed from the healthcare system. It is this reason for a threshold value. The healthcare system will pay so much and no more. That is why cancer patients are problematic. They are terminal if not treated and it will cost less not to treat. Therefore, they are at the mercy of the threshold value.

Discussion

Because of the policy implications related to healthcare, comparative effectiveness analysis should be done very carefully. When implemented, the use of comparative effectiveness can and has lead to the rationing of care as economic value is placed on the life of an individual, and that economic value is used to determine cost effectiveness. The definition of quality adjusted life years should take patient input into consideration, and this input should reflect patient sentiment as opposed to an economically-imposed definition. Moreover, the total cost of decisions should be considered rather than to focus just on the cost of medications. SAS and the preprocessing available in the SAS data step and in SQL procedures can be used to investigate the totality of care. Health outcomes research generally can benefit from the use of SAS.

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